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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/794,851	02/04/97	BARANY, F	19603/461(CR

HM12/0803

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EXAMINER	
RICIGLIANO, J	
ART UNIT	**PAPER NUMBER**
1627	29

DATE MAILED: 08/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/794,851	Barany et al.
Examiner	**Group Art Unit**
Joseph W. Ricigliano	1627

☒ Responsive to communication(s) filed on *May 23, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-43, 45-66, 75-80, 82-88, and 138-151* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-43, 45-66, 75-80, 82-88, and 138-151* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *27*

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. This action is responsive to the amendment of 8/25/99 (paper number 20).

2. Claims 1-43, 45-80 and 82-88 and 138-148 were previously pending in the instant application. Claims 67-74 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. New claims 149-151 have been added. Claims 1-43, 45-66, 75-80, 82-88 and 138-151 are currently being examined on their merits.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-148 and newly added claims 149-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* [US 5, 415, 839], Guo *et al* (1994) and Reddy [US 5,648,213]

See the teachings of Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* [US 5, 415, 839] and Guo *et al* (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-148 under 35 U.S.C. 103(a) as being in the office action of 12/16/97, paper number 7 and the office action of 11/10/98, paper number 17.

The claims as amended on 3/1/99 (paper number 20) required that the first probe have an oligonucleotide target-specific portion and an oligonucleotide addressable array specific portion which were distinct from each other. The rejection of the claims as being unpatentable over

Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* (US 5, 415, 839), Guo *et al* (1994) was previously withdrawn specifically because this limitation was not met or fairly suggested by the Wiedmann, Barany, Zaun and Guo references as combined (see paragraph 9 of the office action of 6/8/99, paper number 21).

However, Reddy *et al* teach the use of oligonucleotide pairs in detecting analytes. Reddy specifically teach that it is advantageous to substitute double stranded oligonucleotide pairs for antibody-antigen pairs when conducting assays in which one member of the pair is attached to the analyte and the other is attached support. Upon contacting under hybridization conditions the double stranded complex forms and the oligonucleotide analyte conjugate is removed from solution by being specifically bound to the corresponding support bound member of the oligonucleotide pair (See the abstract and column 1 lines 1-62).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to substitute an oligonucleotide pair for the antibody antigen capture pair utilized in the references as combined because Reddy *et al* teach using hybridizable oligo-nucleotide pairs for the capture of analytes on a solid phase support. One of ordinary skill in the art would have been motivated to do so because Reddy teaches the advantages of using oligonucleotide capture reagents in the detection of analytes including the ability to reuse the oligonucleotide labeled supports. One of ordinary skill would reasonably have expected to be successful because Reddy had previously utilized oligonucleotides to capture oligonucleotide labeled analytes.

5. Claims 6-10, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* [US 5, 415, 839], Guo *et al* (1994) and Reddy [US 5,648,213] as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-148 *supra* in further view Telenti et al

See the teaching of Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* [US 5, 415, 839], Guo *et al* (1994) and Reddy [US 5,648,213] *supra.*

The references as combined above fail to teach the quantitation of nucleotide amplification reaction products by providing a known amount of a nucleotide sequence as an internal standard.

Telenti et a l (1992) teach that PCR, another nucleotide amplification reaction, can be quantitated by providing a known amount of an internal standard sequence (abstract, page 259).

It would have been *prima facia* obvious at the time the invention was made to one of ordinary skill in the art to combine the use of an internal standard as a quantitation method as taught by Telenti *et al* for the quantitation of PCR products with the ligase amplification reaction as taught by the references as combined *supra*, because Telenti *et al* taught the use of internal standards (or "competitive strands" as they are sometimes called by others) for quantitation of nucleic acid amplification products. One of ordinary skill in the art would have been motivated to do so to obtain a direct assessment of the amount of target present in their assay samples and to be able to normalize the sample results for quantitative comparison.

6. Claims 78, 82, 84-86 are rejected under 35 U.S.C. 103(a) as being unpatentable Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* [US 5, 415, 839], Guo *et al* (1994) and Reddy [5,648,213] as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 under 35 U.S.C. 103(a) *supra* and further in view of Sambrook *et al.*

See the teaching of Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun *et al* [US 5, 415, 839], Guo *et al* (1994) and Reddy [US 5,648,213] *supra.*

The references as combined above fail to teach methods of hybridization the stripping of blots (oligonucleotide arrays) for reuse or the use of exonuclease.

Sambrook *et al* teach hybridization of Southern-blots using oligonucleotide probes and the use of nucleotides (sheared and denatured salmon sperm DNA) between target oligonucleotides to which probes do not bind with specificity (pages 9.47-9.55). Sambrook also teaches the cleaning (or stripping) of Southern blots (page (9.58) and the use of exonuclease (see page 5.78-5.79 and 5.84-5.85).

It would have been *prima facia* obvious at the time the time the invention was made to one of ordinary skill in the art to employ: the conditions for hybridizing oligonucleotide probes to immobilized nucleotides (e.g., Southern-blots etc) including barrier oligonucleotides and exonuclease in the stripping of blots as taught by Sambrook *et al* with the LDR methods as taught by the references combined *supra*, because Sambrook et al had taught Southern blot techniques and the use of exonuclease to digest DNA. One of ordinary skill in the art would have been

motivated to use these methodologies in order to obtain clear specific hybridization of nucleotide probes to immobilized target nucleotides with a low background and to be able to reuse the immobilized array of nucleotides (as taught by the Reddy reference) which can be difficult, time consuming and expensive to prepare.

Response to Arguments

7. Applicants' arguments filed 5/23/00 have been fully considered but they are not persuasive. Applicants review of the teaching of the reference is noted. Applicants argue that the references are not combinable and even if combined do not teach the method of the instant claims.

The arguments are based upon the assertion that there is no motivation to combine the references and when combined the references do not arrive at arrays configured so that the addressable array specific portion and the target specific portion minimize certain undesirable hybridizations. These arguments are not found persuasive because the method is fundamentally two methods combined: a detection reaction using ligase mediated detection to produce a labeled oligonucleotide product and detection of the labeled product on an immobilized nucleotide array.

The references directed to the production of the labeled product are combinable as they are in the same field of invention and motivation to combine them was set forth in the rejections of record. Moreover, detection of the labeled products on oligo nucleotide arrays is also part of the same field of endeavor but is recognized as being an efficient means by which to detect a series of labeled oligonucleotides as set forth by the references as combined.

The argument that the references do not teach quantification as required by claim 11 is not found persuasive because the amount of target is proportionate to the amount of labeled produced, which is detected by the incorporated label, see for example the Guo reference which discusses quantitative image analysis on page 5462 for example. In addition the argument that the references do not teach determination of multiple allele differences as required by claims 12 and 14-34 is not persuasive because detection of alleles is exemplified by Guo et al, and discussed in the other references which renders detection of multiple alleles obvious. The argument that the references do not explicitly recite the use of target specific probes with the same melting point is also not persuasive as one of ordinary skill in the art would recognize that in order to thermocycle a series of reactions the probes need to behave as closely as possible to each other so that the detection reactions (ligase or polymerase mediated) could be conducted together in multiplex format which as the references discuss is desirable.

Applicants' argue that the Telenti reference does not teach the use of internal standards with LDR assays and does not over come the deficiencies of the references it is combined with. This argument is not found persuasive because Telenti teaches the use of standards for amplification reactions, is known in molecular biology which renders them obvious in the method of the instant claims. Moreover, the use of an internal standard is in effect a form of positive control, and the use of positive controls is well established throughout the sciences and molecular arts.

Applicants further argument that neither the Telenti or Sambrook references teach the use of LDR with arrays and that they do not cure the deficiencies of the references which they

are combined with is not found persuasive as the Telenti or Sambrook references were not cited for teaching LDR with arrays the references they were combined with teach the use of LDR with arrays.

Therefore, the rejection is maintained for the reasons above and for the reasons of record. Applicants' assertion that the references fail to teach ligation at a base adjacent to a ligation junction is not found persuasive because one of ordinary skill in the art would recognize that it is obvious that any mismatch at a position close enough to the disrupt the ligation junction would result in interference with the ligation reaction.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-43, 45-66, 75-80, 82-88 and 138-149 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-43, 45-66, 75-80, 82-88 and 138-149 require the detection where in the oligonucleotide probe sets and the arrays are comprised of sequences which minimize the hybridization specific interactions. However, ascertaining the metes and bounds of the claims requires determining the degree of minimization required to meet the limitation of the claim. In

the absence of a specific teaching by which one would be able to ascertain the requisite degree required, one cannot determine the metes and bound of the invention as claimed or if the claims have been infringed.

10. The term "minimize" in claims 1-43, 45-66, 75-80, 82-88 and 138-149 is a relative term which renders the claim indefinite. The term "minimize" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) and Guo *et al* (1994) taken together in view of either Wallace [US 5,981,176 or WO 93/25563] or Davis [5,391,480 or WO 90/11372].

Wiedmann *et al*, under the heading "Theory of LCR (Ligase Chain Reaction) and Similar Amplification Methods" teach "Ligase Detection Reaction (LDR) is similar to LCR" (page S51). Wiedmann *et al* teach ligase detection assays employing primers that are complementary to the sequences to be detected and having a mismatch at the ligation junction for alternate alleles (see figure 2). Moreover, Wiedmann *et al* teach "LDR may be used following a primary amplification

(PCR, 3SR, QB-replicase, RT-PCR) and has the advantage of accurately quantitating the ratio of two alleles in a target sample. LDR coupled to PCR has promise in a multiplex format where several mutations are analyzed in a single amplification"(page S52). Wiedmann *et al* also teaches the used of LCR include genetic diseases (including single base pair variations in alleles, sickle cell anemia and cystic fibrosis) bacteria and viruses ("Current Applications of LCR" starting on page 58 and Table 3). Wiedmann *et al* also teaches the use of LCR and LDR in relation to oncogenes and cancer (Detection of Other Target Sequences, S61). Wiedmann *et al* teach the use of numerous detection methods for ligase mediated nucleic acid amplification products including isotopic, affinity, luminescence and florescence techniques, and in addition, quantitation of products labeled with fluorophores and the use of multiple fluorophores simultaneously (see Detection Methods for LCR Products starting on page S57 and the last paragraph on page S60). Wiedmann *et al* discusses the use of microtiter plate formats in the detection of ligase mediated amplification reaction products on page S58. Last, Wiedmann *et al* also teach multiplex LCR employing as many as six primers simultaneously under the heading of Detection of Genetic Diseases on page S59).

While Wiedmann *et al* teaches LDR and the closely related LCR technique are similar and that multiplexing can be employed with LCR reactions, Wiedmann *et al* does not exemplify multiplexing or oligonucleotide probes as taught in the application or the use of thermostable ligases. Wiedmann *et al* also fails to teach the use of nucleotide amplification reactions for forensic testing, evaluation of cancer and oncogenesis or environmental testing, the use of probes

with an addressable arrays specific portion and the use of nucleotide arrays for their detection and correlation.

Barany (1991a) teaches ligase detection assay as a sensitive assay for detecting and DNA sequences with high sensitivity in the presence of excess DNA (page 7, column 3 through page 8 column 1). Barany (1991a) specifically teaches "From a variety of exceedingly sensitive assays first described for ligase, it was readily apparent that this enzyme could serve as a reporter for the presence of two adjacent strands of DNA hybridized to a complementary strand." (column 3, page 7), which reads on the detection of any target strand provided the target strand sequence is known. Barany goes on to teach "Thermostable ligase discriminated single-base mismatches under both LDR (ligase detection reaction; using two adjacent probes) and LCR (ligase chain reaction; using two pairs of adjacent probes) conditions, with a signal to noise ration ranging from 75 to grater than 500" (starting last paragraph of page 7). Indicating that even the subtlest single-base changes (found in some allelic variations) can be detected. Moreover, Barany (1991a) teaches radioactive, fluorescent, chemiluminescent fluorescent or enzymatic reporter groups are compatible with the closely related technique, ligase chain reaction (page 11, column 1) and several fluorescent probes (page 11, column 3). Barany also teaches that ligase chain reaction could detect a numerous mutations through a multiplexing format and that detection of multiple mutations "could allow for rapid testing of several hundred polymorphic disease mutations in a given gene (page 11, column 3). In table 1 (page 9) Barany teaches LCR reaction conditions where denaturation is carried out at 85 or 94 °C for 0.5 to 1 minute, using probes from 20-28 nucleotides long, wherein the target specific portion of the probes have a hybridization

temperature in the range of 50-85 °C in one example and 62- 94 °C in two other examples, the cycle times range from 0.85 - 5 minutes and 20 to 40 cycles are used in the presence of carrier DNA. Barany *et al* teach T. aquaticus and T. thermophilus ligases as thermostable ligases for use in LDR (page 7 columns 2 & 3). Last, Barany teaches that "Thermostable ligase will only ligate primers that are perfectly complementary to their target sequence and hybridize directly adjacent to each other..."(Figure 4 legend, page 11).

Guo *et al* teaches a multiplex method of amplifying and detecting target nucleic acids applied to genetic polymorphisms. In the method of Guo *et al* the amplified nucleic acids are detected using fluorescently labeled tags on an immobilized oligonucleotide array (see abstract). Guo *et al* also teaches the direct quantitation using fluorescence scanning and video imaging (see the example of Guo *et al* on the simultaneous analysis of four tyrosinase single base mutations, pages 5460-5463). Last Guo teaches "One can readily envision the commercial production of DNA "chips" configured for tissue typing, cancer diagnosis, genetic identity testing, soil and environmental testing and many other applications"(page 6454).

Wallace (for the sake of brevity only the pages of the US patent have been cited although WO document also contains the same teachings) teaches that during nucleic acid amplification reactions it is known to prepare primers with an oligonucleotide portion that can be hybridized to specific locations on an array of oligonucleotides and used for the detection of the amplified product. See for example the abstract and figures 2 and 3. The portion of the primer which is directed to nucleotide the nucleotide array is distinct from the target specific portion so that detection on specific array locations can be conducted as required by the claims as amended.

Davis *et al* (for the sake of brevity only the portions of the US patent have been cited although WO document also contains the same teachings) teach that teaches that during nucleic acid detection it is known to use primers which employ an oligonucleotide portion that can be hybridized to specific locations on an array of oligonucleotides (a "unique tail sequence") and that this sequence can be used for the detection of the nucleic acid produced. See for example the abstract. See figures 1-4, note the embodiment set forth in figure 3 which employs a tail sequence (item 26) and its use on an array in figure 4. The portion of the primer which is directed to nucleotide the nucleotide array is distinct from the target specific portion so that detection on specific array locations can be conducted as required by the claims as amended.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to attach an oligonucleotide portion that can be hybridized to specific locations on an array of oligonucleotides to oligonucleotides used as primer for nucleic acid detection reaction as taught by the Davis and Wallace references in nucleotide detection reactions as taught by the combinations of Wiedmann *et al*, Barany and Guo *et al* because Wiedmann *et al*, Barany and Guo *et al* teach methods for the detection of nucleic acids that result in a labeled product which is subsequently to be detected and both the Davis and Wallace references teach that attachment of an oligonucleotide portion that can be hybridized to specific locations on an array of oligonucleotides permits detection of the product using arrays of complementary nucleic acids. One of ordinary skill in the art would have been motivated to incorporate array specific nucleic acid sequence into the primers used in nucleic acid detection reaction because they permit the concurrent screening for a plurality of labeled products produced in the detection reactions

(see for example Wallace col. 3, lines 2-8). One of ordinary skill in the art would have reasonably expected to be successful because the chemistry for the preparation of labeled primers and detection arrays was well established in the art as were the conditions required for hybridization. Moreover, Davis and Wallace had both previously utilized oligonucleotides to capture oligonucleotide labeled products. Moreover it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to conduct the assays in multiplex format and to use thermostable ligases as taught by the Barany and Guo references because Wiedmann *et al* teaches the use of ligase mediated nucleotide detection reactions and Barany *et al* teaches the use of thermostable ligase for detection reactions and Guo *et al* teaches conducting detection reactions in multiplex format. One of ordinary skill in the art would have been motivated use a thermostable ligase because it permits the cycling of the ligation reactions without having to add subsequent aliquots of ligase which has both the economic benefit of requiring less ligase and the practical benefit of less handling and easy of adaption to automation. One of ordinary skill in the art would have been motivated to conduct multiplex analysis as it permits the rapid determination of genotypes by permitting the determination of specific alleles present in a sample. One of ordinary skill in the art would have reasonably expected to be successful because both thermostable ligase and it use in ligase mediated detection reaction and multiplex analysis has been utilized in the art as evidenced by the references cited.

13. Claims 1-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) and Guo *et al* (1994) taken together in view of either Wallace

[US 5,981,176 or WO 93/25563] or Davis [5,391,480 or WO 90/11372] in further view of either Telenti *et al* or Birkenmeyer [US 5,667,974].

See the teaching of Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) and Guo *et al* (1994) taken together in view of either Wallace [US 5,981,176 or WO 93/25563] or Davis [5,391,480 or WO 90/11372] *supra.*

The references as combined above fail to teach the quantitation of nucleotide amplification reaction products by providing a known amount of a nucleotide sequence as an internal standard.

Telenti *et al*(1992) teach that PCR, another nucleotide amplification reaction, can be quantitated by providing a known amount of an internal standard sequence (abstract, page 259).

Birkenmeyer *et al* teach the use of internal standard nucleic acids for the quantitation of ligase mediated amplification reaction products.

It would have been *prima facia* obvious at the time the invention was made to one of ordinary skill in the art to combine the use of an internal standard as a quantitation method as taught by Telenti *et al* or Birkenmeyer *et al* for the quantitation oligonucleotide amplification products as taught by the references as combined *supra*, because Telenti *et al* and Birkenmeyer *et al* teach the use of internal standards (or "competitive strands" as they are sometimes called by others) for quantitation of nucleic acid amplification products. One of ordinary skill in the art would have been motivated to do so in order to obtain a direct assessment of the amount of target present in their assay samples and to be able to normalize the sample results for quantitative comparison. One of ordinary skill in the art would have reasonably expected to be successful as

the use of internal standards to normalize/ quantitate nucleic acid detection reactions had been used in the art at the time the invention was made.

14. Claims 1-5, 11-21 and 24-43, 45-66, 75-79, 80, 82-88 and 138-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) and Guo *et al* (1994) taken together in view of either Wallace [US 5,981,176 or WO 93/25563] or Davis [5,391,480 or WO 90/11372] and further in view of Sambrook *et al*

See the teaching of Wiedmann *et al* (1994) in view of, Barany (PCR Methods and Applications, 1991a) and Guo *et al* (1994) taken together in view of either Wallace [US 5,981,176 or WO 93/25563] or Davis [5,391,480 or WO 90/11372] *supra.*

The references as combined above fail to teach methods of hybridization the stripping of blots (oligonucleotide arrays) for reuse or the use of exonuclease.

Sambrook *et al* teach hybridization of Southern-blots using oligonucleotide probes and the use of nucleotides (sheared and denatured salmon sperm DNA) between target oligonucleotides to which probes do not bind with specificity (pages 9.47-9.55). Sambrook also teaches the cleaning (or stripping) of Southern blots (page (9.58) and the use of exonuclease (see page 5.78-5.79 and 5.84-5.85).

It would have been *prima facia* obvious at the time the time the invention was made to one of ordinary skill in the art to employ: the conditions for hybridizing oligonucleotide probes to immobilized nucleotides (e.g., Southern-blots etc) including barrier oligonucleotides and exonuclease in the stripping of blots as taught by Sambrook *et al* with the LDR methods as taught

by the references as combined *supra*, because Sambrook *et al* had taught Southern blot techniques and the use of exonuclease to digest DNA. One of ordinary skill in the art would have been motivated to use these methodologies and reasonably expect to be successful in their use as Sambrook *et al* had used them to obtain clear specific hybridization of nucleotide probes to immobilized target nucleotides with a low background and reused the immobilized array of nucleotides which can be difficult, time consuming and expensive to prepare.

Conclusion

15. The examiner thanks applicants representative for bringing the Davis references to his attention in a telephone call on 7/24/00. In order to proceed with more compact prosecution the examiner has cited them on a PTO 892 form rather than having applicant provide a 1449 at such short notice. See the attached interview summary.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached at (703) 308-2439.

J. Venkat

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Joseph W. Ricigliano Ph. D.

July 25, 2000